

REMARKS

The Invention

The invention is based on the identification of T cell epitopes in Japanese pollen allergen molecules. Thus, the invention features peptides containing the T cell epitopes and compositions containing the peptides that are useful in immunotherapy of patients with spring tree pollinosis. The peptides are also useful for diagnosis of spring tree pollinosis.

Status of the Claims

After entry of the amendments made herein, claims 1, 2, 5, 7, 11, 13, 14, 17, and 20-39 will be pending, and claims 1, 5, and 29-39 will be under consideration in this application, claim 3 having been cancelled, claims 2, 7, 11, 13-14, 17, and 20-28 having been withdrawn as allegedly drawn to separate inventions, and new claims 29-39 having been added. New claim 29 differs from claim 1 in that "or a part of said amino acid sequence" is not recited in new claim 29. New claims 30 and 31 are supported by the specification, e.g., in Figure 4. New claim 32 is supported by the specification, e.g., at page 7, lines 17-20. New claims 33-35 are supported by claim 5 as originally filed and by the specification, e.g., at page 15, lines 13-14. New claims 36 and 37 correspond to cancelled claims 18 and 19, respectively. The amendment to claim 1 adding the clause "and optionally a linker sensitive to enzyme cleavage between two epitopes" and new claims 38 and 39 are supported by claim 3 as originally filed and the specification, e.g., at page 13, last paragraph.

Priority Claim

As requested by the Examiner on page 2, paragraph 4, of the Office Action, the specification has been amended to include the appropriate priority claim.

Drawing amendments

Applicants note the Examiner's grant of the proposed amendments to the drawings. As suggested by the Examiner, the Brief Description of the Drawings has been amended to incorporate the SEQ ID NOs added to the drawings by the amendments referred to above.

The Restriction Requirement

The Examiner failed to respond to Applicants' substantive arguments and, instead, reformulated his challenge to unity of invention, citing WO 94/01560 for disclosing a pollen allergen identical to peptide #1-26 recited in claim 1 (SEQ ID NO:28). According to the Examiner, since the "special technical feature" shared by claims 1, 3, 5, 7, 11, 13, 14, 17 and 20-28 does not distinguish over the prior art, the claims lack unity of invention. The Examiner then made the restriction final.

Applicants submit that it is improper for the Examiner to set forth new "grounds of restriction" and simultaneously make such a restriction final. The new grounds were not necessitated by Applicants' amendment; rather, it was necessitated by the Examiner's error. Thus, the restriction requirement should not have been made final and Applicants should be allowed an opportunity to respond. Accordingly, Applicants have canceled peptide #1-26 from claim 1. This amendment obviates anticipation by the WO 94/01560 reference and negates the Examiner's challenge to unity of invention.

Furthermore, with regards to the restriction, Applicants submit that the Examiner has ignored the applicable administrative instructions (as set forth in the MPEP) regarding treatment of dependent claims. Unity of invention is considered only in relation to the independent claims. If the independent claims avoid the prior art and satisfy the requirements of unity of invention, no problem of lack of unity arises with respect to any claims that depend therefrom. In particular, it does not matter if a dependent claim itself contains a further invention. Likewise, no problem arises in cases of a genus/species situation where the genus claim avoids the prior art (MPEP, PCT Administrative Instructions, page AI-53, August 2001; Appendix B).

The instant application contains only two independent claims, i.e., claims 1 and 2. Thus, at most, the application may be divided into two "inventions", wherein Invention I encompasses claim 1 *and its dependents* (e.g., claims 5, 7, 17, 20, 25, 26 and 29-38), directed to Cha o l

peptides and compositions and methods using same, and Invention II encompasses claim 2 *and its dependents* (e.g., claims 11, 13, 14, 21-24, 27, and 28), directed to Cha o 2 peptides and compositions and methods using same. The Examiner's division of the application into twelve distinct inventions is fundamentally in error and directly in conflict with the administrative instructions set forth in the treaty. Specifically, the following groups identified by the Examiner are neither separate nor independent inventions; rather, they comprise further inventions set forth in dependent form:

- Invention III (encompassing dependent claim 7, directed to a method of treating pollinosis using the Cha o 1 allergens of claim 1);
- Invention IV (dependent claim 14, directed to a method of treating pollinosis using the Cha o 2 allergens of claim 2);
- Invention V (dependent claim 17, directed to a method of diagnosing pollinosis using the Cha o 1 allergens of claim 1);
- Invention VI (dependent claims 18-19 (new claims 37 and 38), directed to analogs of the Cha o 1 allergens of claim 1);
- Invention VII (dependent claim 20, directed to a process of making analogs of the Cha o 1 allergens of claim 1);
- Invention VIII (dependent claim 21, directed to a method of diagnosing pollinosis using the Cha o 2 allergens of claim 2);
- Invention IX (dependent claims 22-23, directed to analogs of the Cha o 2 allergens of claim 2);
- Invention X (dependent claim 24, directed to a process of making analogs of the Cha o 2 allergens of claim 2);
- Invention XI (dependent claims 25-26, directed to modified peptides consisting of at least two of the Cha o 1 allergens of claim 1); and
- Invention XII (dependent claims 27-28, directed to modified peptides consisting of at least two of the Cha o 2 allergens of claim 2).

Accordingly, the restriction should be reconsidered and withdrawn in part, with the claims of "Inventions" III, V, VI, VII, and XI being considered with Invention I and the claims of "Inventions" IV, VIII, IX, X, and XII being considered with Invention II.

With regards to the election of species, Applicants reiterate their election of the species of peptide #1-22 (SEQ ID NO:24). However, Applicants remind the Examiner that upon finding the elected species free of art and allowable, he is required to then consider the next species. Applicants await such a finding.

The 35 U.S.C. §112, first paragraph, rejections

Claims 1, 3, and 5 stand rejected on the grounds that (a) the specification allegedly does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims; and (b) that the claims allegedly contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicants understand the Examiner's reasoning with regards to these rejections to be similar and essentially as follows. According to the Examiner, the present claims are so broad as to encompass any peptide comprising at least one or two Class I epitopes selected from the recited group. However, according to the Examiner, the specification discloses only peptides that consist of such epitopes. Furthermore, the Examiner believes that the specification fails to teach how to make and use a peptide that "comprises" such epitopes (i.e., a peptide that may include amino acids in addition to those in the listed epitopes) or a peptide that "comprises" portions of such epitopes. In addition, the specification allegedly fails to describe such modified peptides (modified by addition or deletion). Since the specification fails to provide guidance for or description of what sequences may be added or deleted, it fails to enable and demonstrate possession of the invention as claimed.

Applicants have amended the pending claims to require a peptide "consisting of" one or more of the enumerated allergen epitopes optionally linked by a linker sensitive to enzymatic cleavage. Such an amendment renders moot the Examiner's concerns with regards to enablement and written description of additional sequences..

With regards to the issue of deleted sequences (i.e., for peptides consisting of "a part of said amino acid sequence"), Applicants provide the following remarks. Contrary to the Examiner's characterization, the test for enablement is not "can one predict every species of

compound falling within a claimed genus?" Rather, the test is whether one reasonably skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. See M.P.E.P.2164.01 and United States v. Teletronics, Inc., 857 F.2d 778, 785, 8 USPQ2d 1217, 1233 (Fed.Cir. 1988). For an Examiner to sustain a rejection on the grounds of enablement, he or she must provide evidence that the claimed method could not be performed without undue experimentation.

The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. In fact, there are many factors to be considered when determining whether the specification is enabled and whether any necessary experimentation is "undue". They include: the breadth of the claims; the nature of the invention; the state of the prior art; the level of ordinary skill in the art; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention.

The Examiner quoted Ngo et al. as teaching that "the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance." Applicants point out that Ngo et al. were talking about full-length proteins which of course have unique three-dimensional (tertiary) structures that are determined by their primary structures. The physiological activity of a given full-length protein is dependent on its tertiary structure.

T cell epitopes, on the other hand, are short peptides with an average length of about 15 amino acid residues that bind in the form of an unfolded linear chain to a groove in MHC (HLA for human) class II molecules. A given T cell epitope is presented by a relevant MHC class II molecule to a helper T cell and induces an antigen-specific response in the helper T cell (see page 3, lines 11-15 of the specification). Applicants respectfully submit that the teachings of Ngo et al. in regard to large folded proteins do not apply to short linear peptides such as T cell epitopes, where biological function (binding to MHC and inducing an immune response) has nothing to do with tertiary structure.

Appropriate guidance is provided by the instant specification as to what constitutes "a part of said amino acid sequence" as recited in claim 1 and how to produce such deleted sequences (e.g., page 11, line 3-12 of the specification.). Accordingly, one of ordinary skill in the art could readily determine which epitope fragments are covered by the instant claims (i.e., which ones act as T cell epitopes that are capable of inducing the proliferation of T cells specific for Cha o 1) using the guidance and protocol set forth in the specification. Thus, Applicants submit that claim 1, as it relates to fragments of the listed epitopes that function as T cell epitopes of Japanese cypress pollen allergen Cha o 1 is amply enabled by the instant specification.

The standard for determining compliance with the written description requirement is: "Does the description clearly allow persons of ordinary skill in the art to recognize that the inventor invented what is claimed." The inquiry of whether or not the written description requirement is met is factual and depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. Furthermore, it is well accepted that a specification may, within the meaning of 35 U.S.C. 112, first paragraph, contain a written description of a broadly claimed invention without describing all species that the claim encompasses. The law does not require that the specification describe the exact details for preparing each and every species within the genus described.

In this case, contrary to the Examiner's allegation, the present invention is not directed simply to any fragments, but rather to those fragments of Cha o 1 that function as T cell epitopes. The fact that Applicants do not provide a list of such "functional fragments" is not conclusive on the issue of written description. As discussed above, the number of functional fragments within the scope of the claims is not indefinite. On the contrary: it is readily calculable. Applicants submit that one of ordinary skill in the art would readily recognize that certain amino acid deletions may be made to the noted sequences without eliminating function and that such fragments can be made and tested using conventional techniques and routine experimentation. Accordingly, one of ordinary skill in the art would perceive the broader concept of "functional fragments" from a reading of the instant specification describing short T cell epitope peptides.

In light of the above considerations, Applicants request withdrawal of the rejections under 35 U.S.C. §112, first paragraph.

The 35 U.S.C §102(b) rejection

Claims 1, 3, and 5 stand rejected as allegedly being anticipated by WO 94/01560 ("WO '560").

Applicants understand the Examiner's position to be that WO '560 teaches a peptide, CJI-26, comprising at least one T cell epitope of pollen allergen and consisting of an amino acid sequence identical to that of claimed peptide #1-26 (SEQ ID NO:28). Moreover, the Examiner indicates that the reference teaches a full-length polypeptide comprising SEQ ID NO:28 as well as a pharmaceutical composition containing the full-length polypeptide.

First, it appears from this rejection that the Examiner has withdrawn the species requirement. In response to the Examiner's election of species requirement Applicants provisionally elected with traverse the species of peptide #1-22 (SEQ ID NO:24). However, from the rejection set forth, it appears that the Examiner has considered the claim in its entirety, or at least with respect to peptide #1-26 in addition to peptide #1-22.

In order to anticipate a claim, a single reference must disclose each and every element of the claim. Claim 1 has been amended by the deletion of peptide #1-26 (SEQ ID NO:28) and substitution of "comprising" with "consisting of". Accordingly, as WO '560 fails to disclose any of the peptides recited in the Markush group of claim 1 as amended, it cannot anticipate the claim or its dependents.

In light of the above considerations, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §102(b).

Attached is a marked-up version of the changes being made by the current amendment.

CONCLUSION

In summary, for the reasons set forth above, Applicants maintain that the pending claims patentably define the invention. Applicants request that the Examiner reconsider the rejections as set forth in the Office Action, and permit the pending claims to pass to allowance.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicants' undersigned representative can be reached at the telephone number listed below.

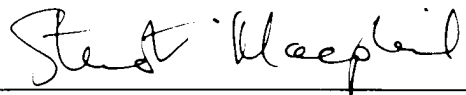
Applicant · Kohsuke Kino et al
Serial No. 09/202,464
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Page 13

Attorney's Docket No. 06501-024001 / M1-805PCT-
US

Enclosed is a Petition for Extension of Time with the required fee. Please charge any other fees or make any credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 5/3/02


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Version with markings to show changes made

In the specification:

On page 1, after the title ("T-CELL EPITOPE PEPTIDES"), insert the following sentence:

--This application claims priority to International Application No. PCT/JP97/02031, filed June 12, 1997.--

The paragraph beginning at page 16, line 2 has been amended as follows:

Figure 2 shows overlapping peptides (#1-1 (SEQ ID NO:3) to #1-28 (SEQ ID NO:30)) of Cha o 1.

The paragraph beginning at page 16, line 4 has been amended as follows:

Figure 3 shows overlapping peptides (#1-29 (SEQ ID NO:31) to #1-35 (SEQ ID NO:37)) of Cha o 1.

The paragraph beginning at page 16, line 11 has been amended as follows:

Figure 6 shows overlapping peptides (#2-1 (SEQ ID NO:38) to #2-27 (SEQ ID NO:64)) of Cha o 2.

The paragraph beginning at page 16, line 13 has been amended as follows:

Figure 7 shows overlapping peptides (#2-28 (SEQ ID NO:65) to #2-51 (SEQ ID NO:88)) of Cha o 2.

In the claims:

Claim 3 has been cancelled.

Claims 1 and 5 have been amended as follows:

1. (Twice amended) A peptide [comprising] consisting of at least one T-cell epitope of Japanese cypress pollen allergen Cha o 1, and optionally a linker sensitive to enzyme

cleavage between two epitopes, wherein each of said epitopes consists [and consisting] of an amino acid sequence selected from the group consisting of Peptide #1-2 (SEQ ID NO:4), Peptide #1-4 (SEQ ID NO:6), Peptide #1-5 (SEQ ID NO:7), Peptide #1-6 (SEQ ID NO:8), Peptide #1-7 (SEQ ID NO:9), Peptide #1-8 (SEQ ID NO:10), Peptide #1-10 (SEQ ID NO:12), Peptide #1-11 (SEQ ID NO:13), Peptide #1-12 (SEQ ID NO:14), Peptide #1-14 (SEQ ID NO:16), Peptide #1-15 (SEQ ID NO:17), Peptide #1-16 (SEQ ID NO:18), Peptide #1-19 (SEQ ID NO:21), Peptide #1-20 (SEQ ID NO:22), Peptide #1-21 (SEQ ID NO:23), Peptide #1-22 (SEQ ID NO: 24), Peptide #1-23 (SEQ ID NO:25), Peptide #1-24 (SEQ ID NO:26), Peptide #1-25 (SEQ ID NO:27), [Peptide #1-26 (SEQ ID NO:28)], Peptide #1-27 (SEQ ID NO:29), Peptide #1-30 (SEQ ID NO:32), Peptide #1-31 (SEQ ID NO:33), Peptide #1-32 (SEQ ID NO:34), Peptide #1-33 (SEQ ID NO:35), and Peptide #1-34 (SEQ ID NO:36) shown in Fig. 4, or a part of said amino acid sequence.

5. (Twice amended) A composition [for peptide-based immunotherapy of pollinosis caused by tree pollen in springtime, comprising] consisting essentially of the peptide of claim 1, as an active ingredient, and a pharmaceutically acceptable diluent or carrier.

Please add new claims 29-39.

--29. The peptide of claim 1, wherein each of said epitopes consists of an amino acid sequence selected from the group consisting of: Peptide #1-2, Peptide #1-4, Peptide #1-5, Peptide #1-6, Peptide #1-7, Peptide #1-8, Peptide #1-10, Peptide #1-11, Peptide #1-12, Peptide #1-14, Peptide #1-15, Peptide #1-16, Peptide #1-19, Peptide #1-20, Peptide #1-21, Peptide #1-22, Peptide #1-23, Peptide #1-24, Peptide #1-25, Peptide #1-27, Peptide #1-30, Peptide #1-31, Peptide #1-32, Peptide #1-33 and Peptide #1-34 shown in Fig. 4.

30. The peptide of claim 1, wherein each of said epitopes consists of an amino acid sequence selected from the group consisting of Peptide #1-2, Peptide #1-7, Peptide #1-8,

Peptide #1-20, Peptide #1-22, Peptide #1-24, Peptide #1-32, Peptide #1-33, and Peptide #1-34 shown in Fig. 4.

31. The peptide of claim 1, wherein each of said epitopes consists of an amino acid sequence selected from the group consisting of Peptide #1-7, Peptide #1-22, Peptide #1-32, and Peptide #1-33 shown in Fig. 4.

32. The composition of claim 5, wherein said pollinosis is Japanese cypress pollinosis and/or cedar pollinosis.

33. A composition consisting essentially of the peptide of claim 29 as an active ingredient, and a pharmaceutically acceptable diluent or carrier.

34. A composition consisting essentially of the peptide of claim 30 as an active ingredient, and a pharmaceutically acceptable diluent or carrier.

35. A composition consisting essentially of the peptide of claim 31 as an active ingredient, and a pharmaceutically acceptable diluent or carrier.

36. An analog peptide consisting of a sequence identical to that of a wild-type peptide of claim 1, except for substitutions in one or more amino acid residues that mediate an interaction with a T cell receptor or that mediate an interaction with a major histocompatibility complex (MHC) class II molecule, wherein the analog peptide simulates a T cell that is responsive to the wild-type peptide.

37. The analog peptide of claim 36, wherein the analog peptide stimulates the T cell to produce a greater amount of interferon- γ than stimulated by the wild-type peptide.

38. The peptide of claim 1, wherein said linker is Arg-Arg or Lys-Lys.

39. A peptide consisting of at least two T-cell epitopes of Japanese cypress pollen allergen Cha o 1 and a linker sensitive to enzyme cleavage between two T-cell epitopes, wherein at least one of said epitopes consists of an amino acid sequence selected from the group consisting of Peptide #1-2 (SEQ ID NO:4), Peptide #1-4 (SEQ ID NO:6), Peptide #1-5 (SEQ ID NO:7), Peptide #1-6 (SEQ ID NO:8), Peptide #1-7 (SEQ ID NO:9), Peptide #1-8 (SEQ ID NO:10), Peptide #1-10 (SEQ ID NO:12), Peptide #1-11 (SEQ ID NO:13), Peptide #1-12 (SEQ ID NO:14), Peptide #1-14 (SEQ ID NO:16), Peptide #1-15 (SEQ ID NO:17), Peptide #1-16 (SEQ ID NO:18), Peptide #1-19 (SEQ ID NO:21), Peptide #1-20 (SEQ ID NO:22), Peptide #1-21 (SEQ ID NO:23), Peptide #1-22 (SEQ ID NO: 24), Peptide #1-23 (SEQ ID NO:25), Peptide #1-24 (SEQ ID NO:26), Peptide #1-25 (SEQ ID NO:27), Peptide #1-26 (SEQ ID NO:28), Peptide #1-27 (SEQ ID NO:29), Peptide #1-30 (SEQ ID NO:32), Peptide #1-31 (SEQ ID NO:33), Peptide #1-32 (SEQ ID NO:34), Peptide #1-33 (SEQ ID NO:35), and Peptide #1-34 (SEQ ID NO:36) shown in Fig. 4, or a part of said amino acid sequence.--